Double patenting

Claims 14-17 were rejected under the judicially created doctrine of obviousness-type double patenting as unpatentable over claims 1-4 of U.S. Patent No. 5,906,828 ("the '828 patent"). Claim 32 was rejected under the judicially created doctrine of obviousness-type double patenting over claim 20 of U.S. Patent No. 6,045,818 ("the '818 patent"). The applicant respectfully traverse the rejections if they are applied to the claims as amended.

Claims 1-4 of the '818 patent define a method of growing eukaryotic cells which includes the following steps:

(a) bringing into contact the cells and a composition comprising (1) a biocompatible solid substrate, (2) biocompatible branched water soluble polymeric tethers, and (3) growth effector molecules, wherein one end of each tether is covalently linked to the substrate, each tether is able to covalently link more than one growth effector molecule, each growth effector molecule is covalently linked to a distal end of a tether so that the growth effector molecule cannot be internalized by cells attached to the substrate, and the growth effector molecules are attached to the substrate in a concentration effective to enhance the rate of target cell growth over the rate of target cell growth with soluble growth effector molecules and growth effector molecules adsorbed to a substrate, without internalization of the molecules; and

(b) maintaining the contacting cells and composition under conditions and for a time sufficient to cause the cells to grow; wherein the step of bringing into contact comprises administering the composition to a patient in need of cell growth.

Claim 20 of the '818 patent defines a method of testing a compound for an effect on tissue. The method recites the following steps:

(a) bringing into contact the compound to be tested and a composition comprising (1) a biocompatible solid substrate, (2) biocompatible branched water soluble polymeric tethers comprising a polymeric material selected from the group consisting of polyethylene oxide, polyvinyl alcohol, polyhydroxyalkyl (meth)acrylate, polyacrylamide, and starches, (3) growth effector molecules, and (4) growing cells, wherein one end of each tether is covalently linked to the substrate, each tether is able to covalently link more than one growth effector molecule, each growth effector molecule is covalently linked to a distal end of a tether so that the growth effector molecule cannot be internalized by cells attached to the substrate, the growth effector molecules are attached to the substrate in a concentration effective to enhance the rate of target cell growth over the rate of target cell growth with soluble growth effector molecules and growth effector molecules adsorbed to a substrate, without internalization of the molecules, and wherein the growing cells are bound to the growth effector molecules;

(b) incubating the compound and the composition under conditions promoting cell growth; and

(c) observing the cells for any effect not observed in cells not brought into contact with the composition.

wherein the substrate has one of the following materials: glasses, metals, polystyrenes, polyethylene vinyl acetates, polypropylenes, polymethacrylates, polyacrylates, polyethylenes,

polyethylene oxides, polysilicates, polycarbonates, polytetrafluoroethylene, fluorocarbons, nylon, silicon rubber, polyanhydrides, polyglycolic acids, polyhydroxyacids, polyesters, polycapralactone, polyhydroxybutyrate, polyphosphazenes, polyorthoesters, polyurethanes, and combinations thereof.

Claims 14-17 and 32 as amended, in contrast, define a method that requires the end of tether linked to the substrate by an agent such as cyanogen bromide, succinimide, aldehyde, tosyl chloride, avidin-biotin, epoxide, and maleimide, or carbodiimide. As WO 89/05616, the reference cited by the Examiner, clearly indicates, the nature of the linking agent plays an important function in directing the orientation and spacing of the tether and the attached growth effector molecules, which is important for obtaining a substantially optimum activity of the growth effector molecule (see, for example, p. 14, lines 1-19 of WO 89/05616, discussed below). Claims 1-4 of the '828 patent and claim 20 of the '818 patent clearly do not recite nor make obvious this important feature. Therefore, the obviousness-type double patent rejections are inappropriate as applied to the amended claims 14-17 and 32.

Rejection Under 35 U.S.C. § 102

Claims 14-17 were rejected under 35 U.S.C. § 102(b) as anticipated by WO 89/05616 by Bio-Metric Systems, Inc. ("WO 616"). Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

WO 616

WO 616 describes biocompatible coatings formed of (1) a biomolecule, (2) a spacer, and (3) a support surface (p. 4, lines 8-16). The spacer is required to have two linking groups or reactive groups that are different from one another (p. 10, lines 5-6). The reactive group linking the spacer to the support surface is a hydrophobic (p. 11, lines 11-12), and desirably photochemical group (p. 10, lines 9-10). Indeed, all the chemicals listed as proper groups linking the spacer to the support surface are hydrophobic photochemical groups (p. 10, line 13). The hydrophobic nature of the group linking to the support surface is important in providing the desired orientation of the spacer and the biomolecule attached to the spacer (p. 14, lines 1-17).

WO 616 also implicitly defines the reactive group linking the spacer to the biomolecule to be a hydrophilic group. As noted above, WO 616 requires the reactive linking the spacer to the support surface and the one linking the spacer to the biomolecule to be different in nature (p. 10, lines 5-6). WO 616 also stated that the group linking the spacer to the support surface is a desirably hydrophobic photochemical group (p. 10, lines 9-10). WO 616 further states that the biomolecules are generally hydrophilic (p. 13, lines 28-31). Therefore, WO 616 implicitly requires the group linking the spacer to the biomolecule to be hydrophilic. This structure is stated to have a unique and beneficial effect in causing the spacer and the biomolecules to stand away from the comparatively hydrophobic support surface (p. 14, lines 3-17). The thermochemical groups described at p. 11, lines 14-30, if are hydrophilic or water loving, are there suitable for linking the spacer to the biomolecule.

The claimed invention

The amended claims 14-17, in contrast, specifically require the linking agent covalently coupling the tether (spacer) to the substrate (support surface) to be one of cyanogen bromide, succinimide, aldehyde, tosyl chloride, avidin-biotin, epoxide, and maleimide, or carbodiimide. These linking agents are hydrophilic agents but not photochemical groups. As discussed above, these agents are not suitable for linking the spacer to the support surface in WO 616. As such, WO 616 does not anticipate claims 14-17 under 35 U.S.C. 102(b).

Rejection Under 35 U.S.C. § 103

Claims 14-16 were rejected under 35 U.S.C. § 103(a) as obvious over U.S. Patent No. 5,370,681 to Herweck et al. ("Herweck"), in combination with U.S. Patent No. 5,171,264 to Merrill ("Merrill"). Claim 17 was rejected under 35 U.S.C. § 103(a) as obvious over Herweck in combination with Merrill in combination with U.S. Patent No. 5,522,895 to Mikos *et al.* ("Mikos"). Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

It should be noted that the claims in the related patent, U.S. Patent No. 5,906,828, were allowed over this art in view of the amendment to the claims to require an appropriate density of growth factors to enhance growth without internalization of growth factors.

Herweck

Herweck discloses implantable devices for sustained release of a bioactive material, such as a therapeutic agent, a cell type, or a diagnostic agent, into a fluid flow pathway of a patient

(see column 3, lines 14-16 and 30-37). Herweck discloses first coating or modifying the surface with glycoproteins such as fibronectin prior to seeding the device with cells (see column 4, lines 62-68). Herweck discloses that such coating may result in improved adhesion of cells (see column 6, lines 23-29). As recognized by the Examiner, Herweck does not disclose or suggest the use of a tether attaching a growth effector molecule to a substrate but merely coats, or adsorbs, the factor upon the substrate.

Merrill

Merrill discloses star molecules of polyethyleneoxide (PEO) that are biocompatible and demonstrate non-thrombogenic properties. Merrill discloses the type of star molecules that are useful in Applicants' methods, as discussed in the specification at page 7, lines 3-20. Merrill teaches that the star PEO molecules can be attached to an appropriate support surface to prevent the surface from recognition by biopolymers (col. 4, lines 54-57). The star PEO molecules can then be attached to an antibody that selectively recognizes its antigen (col. 4, lines 61-68). Merrill does not describe using PEO molecules as tethers for attaching growth effector molecules.

The combination of Herweck and Merrill

There is no suggestion in either reference to incorporate the teaching of the other reference. Herweck does not suggest that it would be advantageous to tether the factors to the substrate. Merrill does not suggest using the star molecules for tethering growth effector molecules to a substrate.

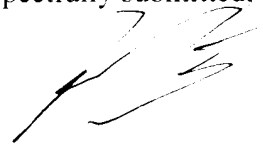
The Examiner asserted that Merrill teaches that the POE molecules are non-thrombogenic, and that thrombogenesis would be a concern for Herweck because the implants in Herweck will also be in blood contact. Because it would be desirable to prevent thrombogenesis in Herweck, it would be desirable to combine Herweck and Merrill. This conclusion, however, is based on the examiner's use of hindsight justification, not from a reading of the references, as required under 35 U.S.C. 103.

Nonetheless, even if the teachings of the references are combined, the combination does not suggest the claimed methods because it does not suggest attaching growth effector molecules with tethers to a substrate in a concentration effective to enhance cell growth in the absence of internalization, nor the specifically recited chemical linkages. Nor do Herweck and Merrill in combination disclose attaching a growth factor molecule to the tether to **prevent internalization of the growth effector molecule**. Note, providing growth effector molecules to cells to stimulate cell growth without internalization of the growth effector molecules is an important feature of the claims in the present application (p. 5, lines 23-30). The assertion that Herweck describes cell growth is stimulated by several factors such as fibrinectin at col. 6, lines 23-29 and 33-36 certainly fails to address this important feature of the method defined in the claims. Moreover, because Herweck and Merrill combined fail to recognize this important feature of the claimed method, Herweck and Merrill would not lead one of ordinary skill in the art to arrive at the claimed method. For the same reason, Herweck and Merrill in combination do not lead to an expectation of success using the claimed method.

Claim 17 was rejected over Herweck in view of Merrill and further in view of Mikos. The Examiner conceded that this rejection stands or falls with the rejection of claims 14-16 over Herweck in view of Merrill. Further, Mikos is similar to Herweck, in that it is directed to a matrix for seeding with cells that can be implanted. Mikos also does not disclose or make obvious selecting growth effector molecules, determining the amount required to enhance growth rate when not internalized, nor chemically coupling the molecules to the substrate in a density and with appropriate linkers to result in enhanced growth rates of attached cells. Mikos therefore does not add the elements missing from the Herweck/ Merrill combination. As such, claim 17 is non-obvious over Herweck in view of Merrill and Mikos.

Allowance of claims 14-17 and 32, as amended, is respectfully solicited.

Respectfully submitted,



Zhaoyang Li
Reg. No. 46,872

Date: December 27, 2002

HOLLAND & KNIGHT LLP
One Atlantic Center, Suite 2000
1201 West Peachtree Street
Atlanta, Georgia 30309-3400
(404) 817-8514
(404) 817-8588 (Fax)

Certificate of Mailing Under 37 C.F.R. § 1.8(a)

I hereby certify that this paper, along with any paper referred to as being attached or enclosed, is being deposited with the United States Postal Service on the date shown below with sufficient postage as first-class mail in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

Aisha Wyatt

Date: December 27, 2002

Marked Up Version of Amended Claims

Pursuant to 37 C.F.R. § 1.121(c)(1)(ii)

14. (Twice amended) A method for growing eukaryotic cells comprising

bringing into contact the cells and a composition comprising

a biocompatible solid substrate,

biocompatible polymeric tethers, and

growth effector molecules,

wherein one end of each tether is covalently linked to the substrate and each growth effector molecule is covalently linked to a distal end of a tether so that the growth effector molecule cannot be internalized by cells attached to the substrate, and the growth effector molecules are attached to the substrate in a concentration effective to enhance the rate of target cell growth without internalization of the molecules; and

wherein the one end of each tether covalently linked to the substrate is achieved using an attachment agent selected from the group consisting of cyanogen bromide, succinimide, aldehyde, tosyl chloride, avidin-biotin, epoxide, and maleimide, carbodiimide, and

maintaining the contacting cells and composition under conditions and for a time sufficient to cause the cells to grow,

wherein the step of bringing into contact comprises administering the composition to a patient in need of cell growth.

15. The method of claim 14 wherein the composition is administered by injection, infusion, or implantation.

16. The method of claim 15 wherein the composition is administered by implantation of the composition and wherein the substrate is shaped to match a desired tissue shape.

17. The method of claim 16 wherein the substrate is biodegradable.

32. (Twice amended) A method of testing a compound for an effect on tissue comprising

bringing into contact the compound to be tested and a composition comprising

a biocompatible solid substrate,

biocompatible polymeric tethers,

growth effector molecules, and

growing cells,

wherein one end of each tether is covalently linked to the substrate and each growth effector molecule is covalently linked to a distal end of a tether so that the growth effector molecule cannot be internalized by cells attached to the substrate, [and] the growth effector molecules are attached to the substrate in a concentration effective to enhance the rate of target cell growth without internalization of the molecules, and the end of each tether covalently linked to the substrate is achieved using an attachment agent selected from the group consisting of cyanogen bromide, succinimide, aldehyde, tosyl chloride, avidin-biotin, epoxide, and maleimide, carbodiimide; and wherein the growing cells are bound to the growth effector molecules;

incubating the compound and the composition under conditions promoting cell growth; and

observing the cells for any effect not observed in cells not brought into contact with the composition.

Clean Version of Amended Claims

Pursuant to 37 C.F.R. § 1.121(c)(1)(ii)

14. (Twice amended) A method for growing eukaryotic cells comprising

bringing into contact the cells and a composition comprising

a biocompatible solid substrate,

biocompatible polymeric tethers, and

growth effector molecules,

wherein one end of each tether is covalently linked to the substrate and each growth effector molecule is covalently linked to a distal end of a tether so that the growth effector molecule cannot be internalized by cells attached to the substrate, and the growth effector molecules are attached to the substrate in a concentration effective to enhance the rate of target cell growth without internalization of the molecules; and

wherein the one end of each tether covalently linked to the substrate is achieved using an attachment agent selected from the group consisting of cyanogen bromide, succinimide, aldehyde, tosyl chloride, avidin-biotin, epoxide, and maleimide, carbodiimide, and

maintaining the contacting cells and composition under conditions and for a time sufficient to cause the cells to grow,

wherein the step of bringing into contact comprises administering the composition to a patient in need of cell growth.

15. The method of claim 14 wherein the composition is administered by injection, infusion, or implantation.

16. The method of claim 15 wherein the composition is administered by implantation of the composition and wherein the substrate is shaped to match a desired tissue shape.

17. The method of claim 16 wherein the substrate is biodegradable.

32. (Twice amended) A method of testing a compound for an effect on tissue comprising

bringing into contact the compound to be tested and a composition comprising

a biocompatible solid substrate,

biocompatible polymeric tethers,

growth effector molecules, and

growing cells,

wherein one end of each tether is covalently linked to the substrate and each growth effector molecule is covalently linked to a distal end of a tether so that the growth effector molecule cannot be internalized by cells attached to the substrate, the growth effector molecules are attached to the substrate in a concentration effective to enhance the rate of target cell growth without internalization of the molecules, and the end of each tether covalently linked to the substrate is achieved using an attachment agent selected from the group consisting of cyanogen bromide, succinimide, aldehyde, tosyl chloride, avidin-biotin, epoxide, and maleimide, carbodiimide; and wherein the growing cells are bound to the growth effector molecules;

incubating the compound and the composition under conditions promoting cell growth; and

observing the cells for any effect not observed in cells not brought into contact with the compositio